Reviewer’s report

Title: LAM-ELISA shows a low sensitivity for the diagnosis of pulmonary tuberculosis in urine

Version: 1 Date: 22 May 2009

Reviewer: Stephen Lawn

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Studies are clearly needed to provide further evaluation of the diagnostic utility of this commercially available urinary LAM ELISA for TB diagnosis and the identification of patient groups in which the assay would be most useful. This study of symptomatic TB suspects in Tanzania includes both HIV+ and HIV- patients in which there were 69 culture-confirmed TB diagnoses, 45 patients with NTM, 82 with negative TB investigations and clinical improvement during follow-up.

Compulsory revisions:

My overall impression is that useful data arise from this study that are broadly consistent with the findings from similar studies presented at recent international conferences (eg CROI Feb 2009, Montreal). However, the way in which the Results section is presented is not logically ordered and could be improved considerably (see below). Once the Results section is better ordered, then the Discussion section might reasonably follow a similar structure.

Title: I would alter the title…. “….diagnosis of pulmonary tuberculosis in urine” reads as rather oddly! Perhaps a ‘Low sensitivity of a urine LAM ELISA in the diagnosis of pulmonary TB’ would be better.

The Results section could be greatly improved if it were divided into sections with appropriate sub-headings, thereby achieving a more ordered and logical flow. These sections should include I) descriptive characteristics of the overall cohort. II) overall prevalence of TB and categorisation of patients into various TB diagnostic groups. III) performance characteristics of LAM in these groups. IV) associations between LAM and patient characteristics.

Table 1 should include all the baseline characteristics of the 291 study participants ie include sex, age. Were patients’ weight, height and BMI measured? It might be interesting to examine this as an index of TB severity / HIV and a co-variate in multivariate analysis of risk factors for LAM+ TB. Were any of the female patients pregnant as this might affect proteinuria / renal function?

It is confusing to have groups designated ‘B’ and ‘B NTM’. Patients in the former have proven TB whereas patients in the latter do not and should therefore be given a completely different group designation.
Table 3. Numerators as well as denominators should be given throughout.

Figure 1. What does ‘adjacent values’ mean with reference to the ‘whiskers’ in this plot. If the whiskers represent the range of values, then Figure 1 and Table 3 do not appear to agree eg for groups B, C and D.

Table 5. I would not restrict this analysis to urine findings as these may well be confounded by other patient variables; age, sex, HIV status, CD4 count, WHO clinical stage of disease, PTB vs EPTB, BMI, sputum smear status etc. The finding that female were more likely to have positive LAM results may be confounded by HIV-status as I presume that a greater proportion of the HIV+ patients were women.

Discussion, paragraph 2, sentence 3. Instead of giving P values, it would be more appropriate simply to state the proportions of patients in these 2 groups in the previous study.

Re specificity of LAM – the findings in the B NTM group do not appear to differ significantly from group C might suggest that the poor specificity found was not attributable to cross-reactivity with NTM. This should be discussed.

The strengths and limitations of the study are not adequately discussed.

If accurate, one of the really important findings is the low specificity of the assay as this is potentially a great limitation to the use of this assay. The LAM+TB-patients could either be (i) true false positives or (ii) the result from misclassification of TB patients as TB-free.

With regard to (ii), it can be very difficult to exclude active TB, especially in HIV+ patients and especially those with advanced immunodeficiency. Diagnostic tools are particularly limited in these patients and even with prospective follow-up, an HIV+ with a chest infection may appear to improve on antibiotic therapy (and be designated TB-free) but also have underlying TB. In this respect it would be useful to analyse the characteristics of the LAM+TB- patients. Were such patients more likely to be HIV+ low CD4 patients?

Another potential source of misclassification of LAM+ patients as TB-free would be if there were problems with the diagnostic gold standard for TB. More information should be given re the QA/QC of the labs, the proportions of cultures lost due to contamination etc.

Minor revisions

Methods: Over what period were the multiple clinical samples collected?
It is unclear why 2 separate urine samples were obtained. Were these on the same day or on different days? What was the agreement between the results?

Methods: Were any of the HIV-infected patients receiving antiretroviral therapy?

Table 1. It is striking that most patients had prolonged symptoms (>3 months).
The authors might comment on this with regard to the likely advanced state of TB in view of the very late presentation.

Figure 2 legend. Error – N for each category in Table 3 (not 2).

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

'I declare that I have no competing interests'